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(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 90 Green Meadow Drive, Tewksbury, MA 01876 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). EVANS, Cheryl; Apartment #21, 35 Bellvista Road, Brookline, MA 02146 (US). BOWMAN, Michael; 50 Aldrich Road, Canton, MA 02021 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US).

(74) Agent: SPRUNGER, Suzanne, A.; Genetics Institute, Inc., 87 CambridgePark Drive, Cambridge, MA 02140 (US).

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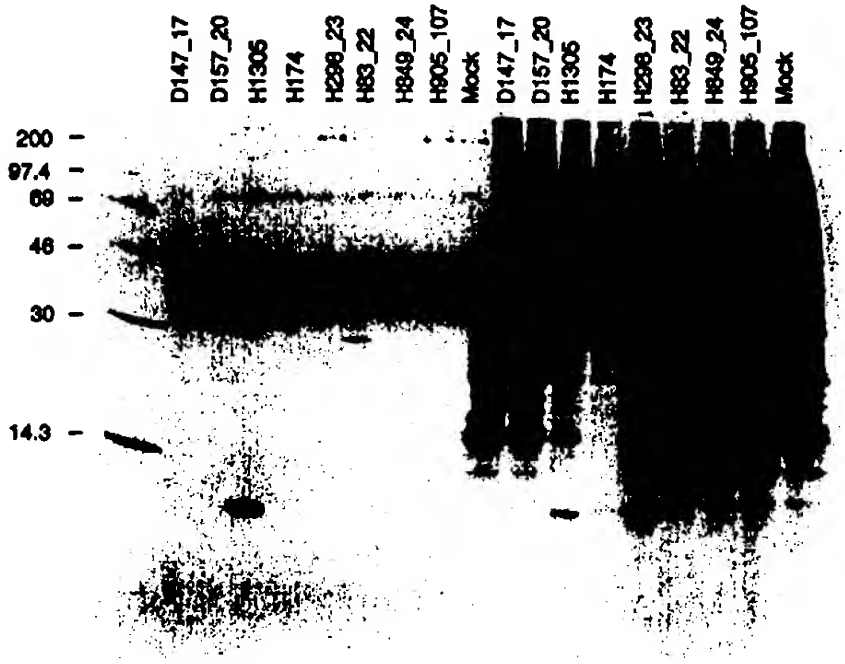

(57) Abstract

The invention provides 13 clones "AZ302-1" isolated from human colon; "AU139-2", "AU105-14", and "AJ147-1" from human adult testes; "AS268-1", "AS264-3", "AS301-2", "AS162-1" AND "AS86-1" from human fetal brain; "D147-17" from human PBMC ; "075-9" from human dendritic cells; "AM262-11" from human fetal kidney and clone "AR28-1" from human adult retina comprising polynucleotides encoding secreted proteins, using methods selective for cDNAs encoding secreted proteins.

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POLYNUCLEOTIDE ENCODING SECRETED PROTEINS

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2 from nucleotide 351 to nucleotide 506;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AZ302_1 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AZ302_1 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AZ302_1 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AZ302_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:3;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:3 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:2 from nucleotide 351 to nucleotide 506; the nucleotide sequence of the full length protein coding sequence of clone AZ302_1 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AZ302_1 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AZ302_1 deposited under accession number ATCC 98076.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:2, SEQ ID NO:1 or SEQ ID NO:4.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:3;

(b) fragments of the amino acid sequence of SEQ ID NO:3; and

(c) the amino acid sequence encoded by the cDNA insert of clone AZ302_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:3.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 23 to nucleotide 517;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AU139_2 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AU139_2 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AU139_2 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AU139_2 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 23 to nucleotide 517; the nucleotide sequence of the full length protein coding sequence of clone AU139_2 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AU139_2 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AU139_2 deposited under accession number ATCC 98076. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 35 to amino acid 115.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5 or SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 35 to amino acid 115;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone AU139_2 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 35 to amino acid 115.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 288 to nucleotide 629;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 441 to nucleotide 629;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AU105_14 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AU105_14 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AU105_14 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AU105_14 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:9 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:8 from nucleotide 288 to nucleotide 629; the nucleotide sequence of SEQ ID NO:8 from nucleotide 441 to nucleotide 629; the nucleotide sequence of the full length protein coding sequence of clone AU105_14 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AU105_14 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AU105_14 deposited under accession number ATCC 98076. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9 from amino acid 25 to amino acid 44.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:8 or SEQ ID NO:10.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:9;

(b) the amino acid sequence of SEQ ID NO:9 from amino acid 25 to amino acid 44;

(c) fragments of the amino acid sequence of SEQ ID NO:9; and

(d) the amino acid sequence encoded by the cDNA insert of clone AU105_14 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:9 or the amino acid sequence of SEQ ID NO:9 from amino acid 25 to amino acid 44.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 164 to nucleotide 298;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS268_1 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS268_1 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS268_1 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS268_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 164 to nucleotide 298; the nucleotide sequence of the full length protein coding sequence of clone AS268_1 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AS268_1 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AS268_1 deposited under accession number ATCC 98076.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11 or SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) fragments of the amino acid sequence of SEQ ID NO:12; and

(c) the amino acid sequence encoded by the cDNA insert of clone AS268_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 254 to nucleotide 681;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone D147_17 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone D147_17 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone D147_17 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone D147_17 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 254 to nucleotide 681; the nucleotide sequence of the full length protein coding sequence of clone D147_17 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone D147_17 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone D147_17 deposited under accession number ATCC 98076. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 73 to amino acid 129.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15, SEQ ID NO:14 or SEQ ID NO:17.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 73 to amino acid 129;

(c) fragments of the amino acid sequence of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone D147_17 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 73 to amino acid 129.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 28 to nucleotide 388;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 76 to nucleotide 388;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone O75_9 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone O75_9 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O75_9 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O75_9 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:18 from nucleotide 28 to nucleotide 388; the nucleotide sequence of SEQ ID NO:18 from nucleotide 76 to nucleotide 388; the nucleotide sequence of the full length protein coding sequence of clone O75_9 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone O75_9 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone O75_9 deposited under accession number ATCC 98076.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:18 or SEQ ID NO:20.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) fragments of the amino acid sequence of SEQ ID NO:19; and

(c) the amino acid sequence encoded by the cDNA insert of clone O75_9 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:19.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 75 to nucleotide 419;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 132 to nucleotide 419;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ147_1 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ147_1 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ147_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ147_1 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:21 from nucleotide 75 to nucleotide 419; the nucleotide sequence of SEQ ID NO:21 from nucleotide 132 to nucleotide 419; the nucleotide sequence of the full length protein coding sequence of clone AJ147_1 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AJ147_1 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AJ147_1 deposited under accession number ATCC 98076.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:21 or SEQ ID NO:23.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) fragments of the amino acid sequence of SEQ ID NO:22; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ147_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:22.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 69 to nucleotide 377;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 120 to nucleotide 377;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AM262_11 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AM262_11 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AM262_11 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AM262_11 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:25;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:25 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:24 from nucleotide 69 to nucleotide 377; the nucleotide sequence of SEQ ID NO:24 from nucleotide 120 to nucleotide 377; the nucleotide sequence of the full length protein coding sequence of clone AM262_11 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AM262_11 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AM262_11

deposited under accession number ATCC 98076. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:25 from amino acid 14 to amino acid 81.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:24.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:25;

(b) the amino acid sequence of SEQ ID NO:25 from amino acid 14 to amino acid 81;

(c) fragments of the amino acid sequence of SEQ ID NO:25; and

(d) the amino acid sequence encoded by the cDNA insert of clone AM262_11 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:25 or the amino acid sequence of SEQ ID NO:25 from amino acid 14 to amino acid 81.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 110 to nucleotide 448;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AR28_1 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AR28_1 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AR28_1 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AR28_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:27 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:26 from nucleotide 110 to nucleotide 448; the nucleotide sequence of the full length protein coding sequence of clone AR28_1 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AR28_1 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AR28_1 deposited under accession number ATCC 98076. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27 from amino acid 15 to amino acid 78.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:26 or SEQ ID NO:28.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:27;

(b) the amino acid sequence of SEQ ID NO:27 from amino acid 15 to amino acid 78;

(c) fragments of the amino acid sequence of SEQ ID NO:27; and

(d) the amino acid sequence encoded by the cDNA insert of clone AR28_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:27 or the amino acid sequence of SEQ ID NO:27 from amino acid 15 to amino acid 78.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:30;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:30 from nucleotide 230 to nucleotide 541;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS162_1 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS162_1 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS162_1 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS162_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:31;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:31 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:30 from nucleotide 230 to nucleotide 541; the nucleotide sequence of the full length protein coding sequence of clone AS162_1 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AS162_1 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AS162_1 deposited under accession number ATCC 98076. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:31 from amino acid 5 to amino acid 25.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:30, SEQ ID NO:29 or SEQ ID NO:32.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:31;

(b) the amino acid sequence of SEQ ID NO:31 from amino acid 5 to amino acid 25;

(c) fragments of the amino acid sequence of SEQ ID NO:31; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS162_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:31 or the amino acid sequence of SEQ ID NO:31 from amino acid 5 to amino acid 25.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 202 to nucleotide 467;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 241 to nucleotide 467;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS264_3 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS264_3 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS264_3 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS264_3 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:35;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:35 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:34 from nucleotide 202 to nucleotide 467; the nucleotide sequence of SEQ ID NO:34 from nucleotide 241 to nucleotide 467; the nucleotide sequence of the full length protein coding sequence of clone AS264_3 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AS264_3 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AS264_3 deposited under accession number ATCC 98076.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:34, SEQ ID NO:33 or SEQ ID NO:36.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:35;

(b) fragments of the amino acid sequence of SEQ ID NO:35; and

(c) the amino acid sequence encoded by the cDNA insert of clone AS264_3 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:35.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38 from nucleotide 173 to nucleotide 579;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS301_2 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS301_2 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS301_2 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS301_2 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:39;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:39 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:38 from nucleotide 173 to nucleotide 579; the nucleotide sequence of the full length protein coding sequence of clone AS301_2 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AS301_2 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AS301_2 deposited under accession number ATCC 98076.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:38, SEQ ID NO:37 or SEQ ID NO:40.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:39;

(b) fragments of the amino acid sequence of SEQ ID NO:39; and

(c) the amino acid sequence encoded by the cDNA insert of clone AS301_2 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:39.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:42;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:42 from nucleotide 363 to nucleotide 593;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:42 from nucleotide 483 to nucleotide 593;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS86_1 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS86_1 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS86_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS86_1 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:43;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:43 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:42 from nucleotide 363 to nucleotide 593; the nucleotide sequence of SEQ ID NO:42 from nucleotide 483 to nucleotide 593; the nucleotide sequence of the full length protein coding sequence of clone AS86_1 deposited under accession number ATCC 98076; or the nucleotide sequence of the mature protein coding sequence of clone AS86_1 deposited under accession number ATCC 98076. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AS86_1 deposited under accession number ATCC 98076.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:42, SEQ ID NO:41 or SEQ ID NO:44.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:43;

(b) fragments of the amino acid sequence of SEQ ID NO:43; and

(c) the amino acid sequence encoded by the cDNA insert of clone AS86_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:43.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF FIGURES

Fig. 1 is an autoradiograph demonatrating the expression of D147_17 in COS cells.

Fig. 2 is an autoradiograph deonstrating the expression of AM262_11 in COS cells.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences are reported below for each clone and protein disclosed in the present application. In some instances the sequences are preliminary and may include some incorrect or ambiguous bases or amino acids. The actual nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein

encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence.

For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Because of the partial ambiguity in reported sequence information, reported protein sequences include "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined nucleotide sequence where applicants believe one should not exist (if the nucleotide sequence were determined more accurately).

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplpasmic reticulum.

Clone "AZ302_1"

A polynucleotide of the present invention has been identified as clone "AZ302_1". AZ302_1 was isolated from a human colon (Caco-2 adenocarcinoma) cDNA library using methods which are selective for cDNAs encoding secreted proteins. AZ302_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AZ302_1 protein").

The nucleotide sequence of the 5' portion of AZ302_1 as presently determined is reported in SEQ ID NO:1. An additional internal nucleotide sequence from AZ302_1 as presently determined is reported in SEQ ID NO:2. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:3. Additional nucleotide sequence from the 3' portion of AZ302_1, including the polyA tail. is reported in SEQ ID NO:4.

The nucleotide sequence disclosed herein for AZ302_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AZ302_1 demonstrated at least some homology with an EST identified as "ye83a03.r1 Homo sapiens cDNA clone 124300 5'" at accession number R02197 (BlastN). Based upon homology, AZ302_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AU139_2"

A polynucleotide of the present invention has been identified as clone "AU139_2". AU139_2 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. AU139_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AU139_2 protein").

The nucleotide sequence of the 5' portion of AU139_2 as presently determined is reported in SEQ ID NO:5 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:6. The predicted acid sequence of the AU139_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Additional nucleotide sequence from the 3' portion of AU139_2, including the polyA tail, is reported in SEQ ID NO:7.

The nucleotide sequence disclosed herein for AU139_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AU139_2 demonstrated at least some homology with three ESTs identified as "EST16319 Homo sapiens cDNA 5' end" (accession number T30419, BlastN), "EST04080 Homo sapiens cDNA clone HFBDQ07" (accession number T06191, BlastN), and "EST108441 Rattus sp. cDNA 5'". Based upon homology, AU139_2 proteins and each homologous protein or peptide may share at least some activity.

Clone "AU105_14"

A polynucleotide of the present invention has been identified as clone "AU105_14". AU105_14 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. AU105_14 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AU105_14 protein").

The nucleotide sequence of the 5' portion of AU105_14 as presently determined is reported in SEQ ID NO:8 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:9. The predicted acid sequence of the AU105_14 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:9. Amino acids 1 to 51 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 52. Additional nucleotide sequence from the 3' portion of AU105_14, including the polyA tail, is reported in SEQ ID NO:10.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AU105_14 should be approximately 2670 bp.

The nucleotide sequence disclosed herein for AU105_14 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "AS268_1"

A polynucleotide of the present invention has been identified as clone "AS268_1". AS268_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. AS268_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS268_1 protein").

The nucleotide sequence of the 5' portion of AS268_1 as presently determined is reported in SEQ ID NO:11 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:12. The predicted acid sequence of the AS268_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Additional nucleotide sequence from the 3' portion of AS268_1, including the polyA tail, is reported in SEQ ID NO:13.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS268_1 should be approximately 1800 bp.

The nucleotide sequence disclosed herein for AS268_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AS268_1 demonstrated at least some homology with the rabbit and murine ryanodine receptors (BlastN accession number M59743, BlastX accession number X83933). Ryanodine receptors have recently been shown to be the Ca^{2+} releasr channels of sarcoplasmic reticulum in both cardiac muscle and skeletal muscle. Based upon homology, AS268_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "D147_17"

A polynucleotide of the present invention has been identified as clone "D147_17". D147_17 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. D147_17 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "D147_17 protein").

The nucleotide sequence of the 5' portion of D147_17 as presently determined is reported in SEQ ID NO:14. An additional internal nucleotide sequence from D147_17 as presently determined is reported in SEQ ID NO:15. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is

reported in SEQ ID NO:16. Additional nucleotide sequence from the 3' portion of D147_17, including the polyA tail, is reported in SEQ ID NO:17.

The nucleotide sequence disclosed herein for D147_17 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "O75_9"

A polynucleotide of the present invention has been identified as clone "O75_9". O75_9 was isolated from a human dendritic cells cDNA library using methods which are selective for cDNAs encoding secreted proteins. O75_9 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "O75_9 protein").

The nucleotide sequence of the 5' portion of O75_9 as presently determined is reported in SEQ ID NO:18 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:19. The predicted acid sequence of the O75_9 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:19. Amino acids 1 to 16 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 17. Additional nucleotide sequence from the 3' portion of O75_9, including the polyA tail, is reported in SEQ ID NO:20.

The nucleotide sequence disclosed herein for O75_9 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "AJ147_1"

A polynucleotide of the present invention has been identified as clone "AJ147_1". AJ147_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. AJ147_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ147_1 protein").

The nucleotide sequence of the 5' portion of AJ147_1 as presently determined is reported in SEQ ID NO:21 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:22. The predicted acid sequence of the AJ147_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:22. Amino acids 1 to 19 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 20. Additional nucleotide sequence from the 3' portion of AJ147_1, including the polyA tail, is reported in SEQ ID NO:23.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ147_1 should be approximately 500 bp.

The nucleotide sequence disclosed herein for AJ147_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AJ147_1 demonstrated at least some homology with murine calmegin (Meg 1)/calnexin (BlastN accession number D14117). Calmegin is a Ca^{2+}-binding protein that is specifically expressed in spermatogenesis. The highly regulated, specific and abundant expression of calmegin suggests that it plays an important role in spermatogenesis. Based upon homology, AJ147_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AM262_11"

A polynucleotide of the present invention has been identified as clone "AM262_11". AM262_11 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins. AM262_11 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AM262_11 protein").

The nucleotide sequence of AM262_11 as presently determined is reported in SEQ ID NO:24 What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AM262_11 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:25. Amino acids 1 to 17 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 18.

The nucleotide sequence disclosed herein for AM262_11 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AM262_11 demonstrated at least some identity with the human eotaxin precursor gene and protein (BlastN accession number U34780; this database entry was made subsequent to applicants' isolation of AM262_11). Based upon homology, AM262_11 proteins and each homologous protein or peptide may share at least some activity.

Clone "AR28_1"

A polynucleotide of the present invention has been identified as clone "AR28_1". AR28_1 was isolated from a human adult retina cDNA library using methods which are selective for cDNAs encoding secreted proteins. AR28_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AR28_1 protein").

The nucleotide sequence of the 5' portion of AR28_1 as presently determined is reported in SEQ ID NO:26 What applicants presently believe is the proper reading frame for

the coding region is indicated in SEQ ID NO:27. The predicted acid sequence of the AR28_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:27. Additional nucleotide sequence from the 3' portion of AR28_1, including the polyA tail, is reported in SEQ ID NO:28.

The nucleotide sequence disclosed herein for AR28_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "AS162_1"

A polynucleotide of the present invention has been identified as clone "AS162_1". AS162_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. AS162_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS162_1 protein").

The nucleotide sequence of the 5' portion of AS162_1 as presently determined is reported in SEQ ID NO:29. An additional internal nucleotide sequence from AS162_1 as presently determined is reported in SEQ ID NO:30. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:31. Additional nucleotide sequence from the 3' portion of AS162_1, including the polyA tail, is reported in SEQ ID NO:32.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS162_1 should be approximately 1380 bp.

The nucleotide sequence disclosed herein for AS162_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AS162_1 demonstrated at least some identity with an EST identified as "ym96e05.s1 Homo sapiens cDNA clone 166784 3'" (accession number R88809, BlastN). Based upon identity, AS162_1 proteins and each identical protein or peptide may share at least some activity.

Clone "AS264_3"

A polynucleotide of the present invention has been identified as clone "AS264_3". AS264_3 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. AS264_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS264_3 protein").

The nucleotide sequence of the 5' portion of AS264_3 as presently determined is reported in SEQ ID NO:33. An additional internal nucleotide sequence from AS264_3 as presently determined is reported in SEQ ID NO:34. What applicants believe is the proper

reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:35. Amino acids 1 to 13 of SEQ ID NO:35 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 14. Additional nucleotide sequence from the 3' portion of AS264_3, including the polyA tail, is reported in SEQ ID NO:36.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS264_3 should be approximately 3300 bp.

The nucleotide sequence disclosed herein for AS264_3 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AS264_3 demonstrated at least some weak similarity to collagen. Based upon homology, AS264_3 proteins and each homologous protein or peptide may share at least some activity.

Clone "AS301_2"

A polynucleotide of the present invention has been identified as clone "AS301_2". AS301_2 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. AS301_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS301_2 protein").

The nucleotide sequence of the 5' portion of AS301_2 as presently determined is reported in SEQ ID NO:37. An additional internal nucleotide sequence from AS301_2 as presently determined is reported in SEQ ID NO:38. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:39. Additional nucleotide sequence from the 3' portion of AS301_2, including the polyA tail, is reported in SEQ ID NO:40.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS301_2 should be approximately 2600 bp.

The nucleotide sequence disclosed herein for AS301_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AS301_2 demonstrated at least some homology with ESTs identified as "yp82b08.r1 Homo sapiens cDNA clone 193911 5'" (BlastN accession number R83399), "ye66c02.r1 Homo sapiens cDNa clone 122690 5'", and "ym26e09.r1 Homo sapiens cDNA clone 49167 5'" (BlastN accession number H16691). Based upon homology, AS301_2 proteins and each homologous protein or peptide may share at least some activity.

Clone "AS86_1"

A polynucleotide of the present invention has been identified as clone "AS86_1". AS86_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. AS86_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS86_1 protein").

The nucleotide sequence of the 5' portion of AS86_1 as presently determined is reported in SEQ ID NO:41. An additional internal nucleotide sequence from AS86_1 as presently determined is reported in SEQ ID NO:42. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:43. Amino acids 1 to 40 of SEQ ID NO:43 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 41. Additional nucleotide sequence from the 3' portion of AS86_1, including the polyA tail, is reported in SEQ ID NO:44.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS86_1 should be approximately 2122 bp.

The nucleotide sequence disclosed herein for AS86_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Figs. 1 and 2 are autoradiographs evidencing expression of clones of the present invention. All clones were expressed in COS cells.

Deposit of Clones

Clones AZ302_1, AU139_2, AU105_14, AS268_1, D147_17, O75_9, AJ147_1, AM262_11, AR28_1, AS162_1, AS264_3, AS301_2 and AS86_1 were deposited on June 6, 1996 with the American Type Culture Collection under accession number ATCC 98076, from which each clone comprising a particular polynucleotide is obtainable. Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' cite, EcoRI; 3' cite, NotI) to produce the appropriately sized fragment for such clone (approximate clone size fragment are identified below). Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was

used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
AZ302_1	SEQ ID NO:45
AU139_2	SEQ ID NO:46
AU105_14	SEQ ID NO:47
AS268_1	SEQ ID NO:48
D147_17	SEQ ID NO:49
O75_9	SEQ ID NO:50
AJ147_1	SEQ ID NO:51
AM262_11	SEQ ID NO:52
AR28_1	SEQ ID NO:53
AS162_1	SEQ ID NO:54
AS264_3	SEQ ID NO:55
AS301_2	SEQ ID NO:56
AS86_1	SEQ ID NO:57

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth.

Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida,* or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium,* or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits

for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput

screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one

of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring

proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by

inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science *257*:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected

with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides . For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492,

1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine

et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*.

R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears,

deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to

allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med.

168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color,

eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent

to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical

composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1µg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In

the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose

or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other

known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John
LaVallie, Edward
Racie, Lisa
Merberg, David
Treacy, Maurice
Evans, Cheryl
Bowman, Michael
Spaulding, Vikki

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 57

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genetics Institute, Inc.
(B) STREET: 87 CambridgePark Drive
(C) CITY: Cambridge
(D) STATE: Massachusetts
(E) COUNTRY: U.S.A.
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
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(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Brown, Scott A.
(B) REGISTRATION NUMBER: 32,724

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (617) 498-8224
(B) TELEFAX: (617) 876-5851

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 270 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CTTCNTGNNG CAAAAAACAG AAAACTGGGG NTNNGAAACG TGGGCAGTGT GGTCTTNGNG 60

NGCACTGTAA ATTTGACTTT GTTTNTNTCA CTGAGCGCAT CAGGNATGTC NATTNGGANG 120

GGGGATCNAC ATTCNGGTCC ACAGATACNG ATCTCGGCTT GGGGCGGTCC TCCTCCTGCT 180

GNTGCAGCAA ANCGGGAACC GCGGCCATGG CGACGCGGGA CTCGAGCAGG GCCCGCCTGG 240

CTGTGCGAGG AAAGTAGGCC ATGAAGGCCG 270

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 506 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

TANACTTTCC TTAGTTTTTC AAATAGCTCA NCAACCTTCA ATANNTACTT TTTGATGACT 60

GTGGNNTCTT NTAAANCCAG GNTATGTAAN CAGGCTNCGG TGTGNATATA TTCATCGNCA 120

ACATTTNTAT AAAATCTGKT CATTTTKTCA GCTTTMACAC AAGAATCTTT GATCCTATTG 180

TAATAGTTAA TAAGGAAGTT CTTCTCTTGC TCAAAGAAGT CATCTACCTC CTTAACTCCA 240

GTAAAAAGGA CTTCATCAGC ACTTTTCACC ACACTTTTGA AGAAGCCACC AAACATTTYT 300

TTAGTATTTT TCCGCCTAAC ACTTAGATCC TGATCATATT CCAGGAAAAC ATGAAAGTTG 360

CGATCTTTAC TGAGAACAGG GTGAGAAGAA AGCCGCTGAA GAAAGACTTT CATGGGAGGA 420

CACAGTTYTT CTTAAACACA GCGAGATACT CAGCTTCCAG TTCTTGTTTC ATCTGGGCTT 480

ATTATTCCAC CTTCTCCCAG TTTCTG 506

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
Met Lys Val Ala Ile Phe Thr Glu Asn Arg Val Arg Arg Lys Pro Leu
1               5                  10                  15

Lys Lys Asp Phe His Gly Arg Thr Gln Phe Phe Leu Asn Thr Ala Arg
            20                  25                  30

Tyr Ser Ala Ser Ser Ser Cys Phe Ile Trp Ala Tyr Tyr Ser Thr Phe
        35                  40                  45

Ser Gln Phe
    50
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
TTTTTAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA      60

AAAAAAAAAA AAAAAAAAAA AAAAA                                            85
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 517 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
CAATTGCAGA NTTNGAATTC GGCTTTCATG GCATACGGCY TTCATGGCCT AGGGGAGGAA      60
```

GTTGCCTTGT ACTGTGCCAA ATATCTTCCT GATATCATCA AAGATCAGAA GGCCTACAAG 120

GAAGGCAAGC TACAGAAGGC TTTAGAAGAT GCCTTCTTGG CTATTGACGC CAAATTGACC 180

ACTGAAGAAN TCATTAAAGA GCTGGCACAG ATTGCAGGGC GACCCACTGA GGATGAAGAT 240

GAAAAAGAAA AAGTAGCTGA TGAAGATGAT GTGGACAATG AGGAGGCTGC ACTGCTGCAT 300

GAAGAGGCTA CCATGACTAT TGAAGAGCTG CTGACACGCT ACGGGCAGAA CTGTCACAAG 360

GGCCCTCCCC ACAGCAAATN TGGAGGTGGG ACAGGCGAGG AACCAGGGTC CCAGGGCCTC 420

AATGGGGAGG CAGGACCTGA GGACTCAACT AGGGAAACTC CTTCACAAGA AAATGGCCCC 480

ACAGCCAAGG CCTACACAGG CTTTTCCTCC AACTCGG 517

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 115 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Ala Tyr Gly Xaa His Gly Leu Gly Glu Glu Val Ala Leu Tyr Cys
1 5 10 15

Ala Lys Tyr Leu Pro Asp Ile Ile Lys Asp Gln Lys Ala Tyr Lys Glu
20 25 30

Gly Lys Leu Gln Lys Ala Leu Glu Asp Ala Phe Leu Ala Ile Asp Ala
35 40 45

Lys Leu Thr Thr Glu Glu Xaa Ile Lys Glu Leu Ala Gln Ile Ala Gly
50 55 60

Arg Pro Thr Glu Asp Glu Asp Glu Lys Glu Lys Val Ala Asp Glu Asp
65 70 75 80

Asp Val Asp Asn Glu Glu Ala Ala Leu Leu His Glu Glu Ala Thr Met
85 90 95

Thr Ile Glu Glu Leu Leu Thr Arg Tyr Gly Gln Asn Cys His Lys Gly
100 105 110

Pro Pro His
115

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 406 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TTAGATTGTT TTTNGGCCTT CNGGACCTGA GATTGAGTTT TNTTTTTTTC CTTTAGCNTT 60

AGCAGTGGGN ATGAGGTGNG CAGGGGGAGN TGGGTGGTTN AATCCGCCCA TTCCAAAGAG 120

GGTTNTCCTT CNANANTGCA GCNGGGAGCT TTTGANGTCN TTCCCAGCCG CTTTTGTTCN 180

TNGGGTTNAT NACCGGTTNT GNGCCTGTGT TNTGTTGTGT TGGAGGGAAG GACTGGCGGT 240

TCTGGTTTTT ACTCTGTGAA CTTTATTTAA GGACATTTTT TTTTATTGGG GGGTCCATGG 300

CCCTCGGCCG CTKGCACCCG YTTTTTGTTG WACACTTTCA ATCAACACTT TTTCAGANTA 360

AAGGCCAAAA CCTAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAA 406

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 629 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

CAGTTTTAGA AAGAAGCACC TTGCTGGATA GATTTGGAGG TTTTCTTTTG GAAATTCANA 60

TTCCATATGT GTTTTTTGCA TCTGAAGGAC TTCTTAATAC TCCAGACATA CTTCAGCTGC 120

TAGAATCCAA CTATAACATC TCACTAGTAG AGAGAGGCTG CAGTGAGTCA TTGAAACTCT 180

TTGGAAGTTC AGAGTGTTAT GTAGTGGTGA CAATTGATGA ACACACTGCC ATAATTTTGC 240

AGGATCTARA AGAATTGAAT TGTGAGAAGG CATCAGACAA TATCATTATG AGGCTGATGG 300

CATTATCATT ACAGTACAGA TATTGTTGGA TAATTTTATA TACCAAAGAA ACATTAAATT 360

CAGAGTATCC GCTTACAGAA AAGACACTTC ATCACCTAGC ACTGATTTAT GCAGCTTTGG 420

TTTCATTTGG GCTAAACTCT GAAGAACTGG ATGTAAAGCT TATAATTGCC CCAGGAGTAG 480

AAGCAACTGC CTTGATAATT CGACAAATTG CTGACCACAG TTTAATGACC TCAAAGAGAG 540

ATCCTCATGA ATGGTTGGAT AAATCCTGGC TTAAAGTTTC ACCATCTGAG GAAGAAATGT 600

ACTTACTTGA TTTTNCCATG TATTAACCC 629

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Arg Leu Met Ala Leu Ser Leu Gln Tyr Arg Tyr Cys Trp Ile Ile
1 5 10 15

Leu Tyr Thr Lys Glu Thr Leu Asn Ser Glu Tyr Pro Leu Thr Glu Lys
20 25 30

Thr Leu His His Leu Ala Leu Ile Tyr Ala Ala Leu Val Ser Phe Gly
35 40 45

Leu Asn Ser Glu Glu Leu Asp Val Lys Leu Ile Ile Ala Pro Gly Val
50 55 60

Glu Ala Thr Ala Leu Ile Ile Arg Gln Ile Ala Asp His Ser Leu Met
65 70 75 80

Thr Ser Lys Arg Asp Pro His Glu Trp Leu Asp Lys Se: Trp Leu Lys
85 90 95

Val Ser Pro Ser Glu Glu Glu Met Tyr Leu Leu Asp Phe
100 105

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 280 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TCAAGAAAGT TAAAACTTAG GACAAAATNG AAGTTNGAAA ATTTCCAACT TAAAGTATCA 60

TTTTCTGTAA ACACAATTTA AGAACAAATT ANTAAGAGGA AATATTTGCA ACCCAGATAA 120

TAGGAAAAAA AGTTNACATT TNTCATATAT AAAGAATTCC TACAAATTGA TAGAAAGAAG 180

ACAACNTGAT AGAAGAACGG GCAAAATATA TGAACAGATA TTTCCTCAGA AAAAAACAAA 240

AATTGTCAAT AAACATTTGA AACACAAAAA AAAAAAAAAA 280

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 298 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGAAWAAGAA GAGAAAGCCA AGGAAGACAA GGGCAAACAA AAGTTGAGGC AGCTTCACAC 60

ACACAGATAC GGAGAACCAG AAGTGCCAGA GTCAGCATTC TGGAAGAAAA TCATAGCATA 120

TCAACAGAAA CTTCTAAACT ATTTTGCTCG CAACTTTTAC AACATGAGAA TGTTAGCCTT 180

ATTTGTCGCA TTTGCTATCA ATTTCATCTT GCTCTTTTAT AAGGTCTCCA CTTCTTCTGT 240

GGTTGAAGGA AAGGAGCTCC CCACGAGAAG TTCAAGTGAA AATGCCAAAG TGACAAGC 298

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Arg Met Leu Ala Leu Phe Val Ala Phe Ala Ile Asn Phe Ile Leu
1 5 10 15

Leu Phe Tyr Lys Val Ser Thr Ser Ser Val Val Glu Gly Lys Glu Leu
20 25 30

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 165 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GGAAACATTT TGCTGATTTT GNGAATTGCC AGCGTTGTGT GTTTTCTGGG AGCATNGAAG 60

CTCTGTTTCG GAAGAGCTGT TTCCTCCCCC CACCTTTTGT ATTTACTTTG AGACTAAAGA 120

CNGAAGAATA ATCTAAATTC ATACTCAGAC AAAAAAAAAA AAAAA 165

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 224 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GCTGGGCTCG GGCTCANCTC GACTGGGCTC GGCGGGCGGC GGCGGCGGCG CCCGCGGCTG 60

GCGGAAGAAG GAGGGCGAGG GCGGGCGCGG GCCGGCGGGC GGGCGGAAAA AGGAGGAAAG 120

GCGCGGGGAG CCAGGCCTCG GGGCCTCGGA NCAACCACCC GAGCAGACGG AGTACACGGA 180

GCAGCGGCCC CGGCCCCGCC AACGCTGCCG CCGGGATGCT CCAA 224

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 595 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CTGGCCGCCA GGTAGAGCGT TGGTTCCGTC GCCGCCGCAA CCAGGACCGG CCCAGTNTCN 60

TCAAGAAGTT CCGAGAAGCC AGCTGGAGAT TCACATTTTA CNTGATTGCN TTCATTGCCG 120

GCATGGCCGT CATTGTGGAT AAACCCTGGT TCTATGACAT GAAGAAAGTT TGGGAGGGAT 180

ATCCCATACA GAGCACTATC CNTTCCCAGT ATTGGTACNA CATGATTGAA CTTTCCTTNT 240

ACTGGTGCSC TGCTCTTCAG CATTGCCTCT GATGTCAAGC GAAAGGATTT CAAGGAACAG 300

ATCATCCACC ATGTGKCCAC CATCATTCTC ATCAGCTTTT CCTGGGTTTG CCAATTACAT 360

CCGAGCTGGG ACTCTAATCA TGGCTCTGCA TGACTCTTCC GATTACCTGC TGGAGTCAGC 420

CAAGATGTTT AACTACGCGG GATGGAAGAA CACCTGCAAC AACATCTTCA TCGTCTTCGC 480

CATTGTTTTT ATCATCACCC GACTGGTCNT CCTGCCCTTC TGGNTCCTGC ATTGCACCCT 540

GGTGTNCCCN CTGGAGCTCT ATCCTGCCTT CTTTGGCTNT TACTTCTTCN ATTCC 595

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 129 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Ser Ser Ala Leu Pro Leu Met Ser Ser Glu Arg Ile Ser Arg Asn Arg
1 5 10 15

Ser Ser Thr Met Xaa Pro Pro Ser Phe Ser Ser Ala Phe Pro Gly Phe
20 25 30

Ala Asn Tyr Ile Arg Ala Gly Thr Leu Ile Met Ala Leu His Asp Ser
35 40 45

Ser Asp Tyr Leu Leu Glu Ser Ala Lys Met Phe Asn Tyr Ala Gly Trp
50 55 60

Lys Asn Thr Cys Asn Asn Ile Phe Ile Val Phe Ala Ile Val Phe Ile
65 70 75 80

Ile Thr Arg Leu Val Ile Leu Pro Phe Trp Ile Leu His Cys Thr Leu
85 90 95

Val Tyr Pro Leu Glu Leu Tyr Pro Ala Phe Phe Gly Tyr Tyr Phe Phe
100 105 110

Asn Ser Met Met Gly Val Leu Gln Leu Leu His Ile Phe Trp Ala Tyr
115 120 125

Leu

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 145 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GGTTTTAAAG CCAGAATTAC GGNTAGCACC TAGCATTTCA GCAGAGGGAC CATTTTAGAC 60

CAAAATGTAC TGTTAANGGG TTTTTTTTTA AAATTAAAAG ATTAAATAAA AAATATTAAA 120

TAAAACANGA AAAAAAAAAA AAAAA 145

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 398 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GAATTCGGCC AAANANGCCT AGGCAGAATG GGACTCCAAG CCTGCCTCCT AGGGCTCTTT 60

GCCCTCATCC TCTCTGGCAA ATGCAGTTAC AGCCCGGAGC CCGACCAGCG GAGGACGCTG 120

CCCCCAGGCT GGGTGTCCCT GGGCCGTGCG GACCCTGAGG AAGAGCTGAG TCTCACCTTT 180

GCCCTGAGAC AGCAGAATGT GGAAAGACTC TCGGAGCTGG TGCANGCTGT GTCGGATCCC 240

AGCTCTCCTC AATACGGAAA ATACCTGACC CTAGAAAAAT GTGGCTGATC TGGTGAGGCC 300

ATCCCCACTG ACCCTCCACA CGGTGCAAAA ATGGCTCTTG GCAGCCCGGA NCCCAAAAAT 360

TGCCATTCTG TGATCACACA GGAACTTTCT GACTTGCT 398

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met Gly Leu Gln Ala Cys Leu Leu Gly Leu Phe Ala Leu Ile Leu Ser
1 5 10 15

Gly Lys Cys Ser Tyr Ser Pro Glu Pro Asp Gln Arg Arg Thr Leu Pro
20 25 30

Pro Gly Trp Val Ser Leu Gly Arg Ala Asp Pro Glu Glu Glu Leu Ser
35 40 45

Leu Thr Phe Ala Leu Arg Gln Gln Asn Val
50 55

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 437 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TGCTTCCTTG GGGGTGAGTT TTCATTCACT ATGTGGGGAG GGACCTTACG GGAAAACCCA 60

TGTTGTAAGG TTCCCCCAAA TTCCTACCAG CTTTCCACAG GCCTTGGCCC CCCATGTGGA 120

CTTTGTGGGG GGACTGCACC GTTTTTCCCC CAACATCATC CCTGAGGCAA CGTCCTGAGC 180

CGCAGGTGAC AGGGACTGTA GGCCTGCATC TGGGGGTAAC CCCCTCTGTG ATCCGTAAGC 240

GATACAACTT GACCTCACAA GACGTGGGCT CTGGCACCAG CAATAACAGC CAAGCCTGTG 300

CCCAGTTCCT GGAGCAGTAT TTCCATGACT CAGACCTGGC TCAGTTCATG CGCCTCTTCG 360

GTGGCAACTT TGCACATCAG GCATCAGTAG CCCGTGTGGT TGGACAACAG GGCCGGGGCC 420

GGCCGGCGCA TCTCGAG 437

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 419 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CGGGGACCWA GTGGCAACGA CTTGGACATC TGAGCTGTCA CTGCCGAAAA CAGGCCGCAA 60

GAGAGATAAT CAATATGCAT TTCCAAGCCT TTTGGCTATG TTTGGGTCTT CTGTTCATCT 120

CAATTAATGC AGAATTTATG GATGATGATG TTGAGACGGA AGACTTTGAA GAAAATTCAG 180

AAGAAATTGA TGTTAATGAA AGTGAACTTT CCTCAGAGAT TAAATATAAG ACACCTCAAC 240

CTATAGGAGA AGTATATTTT GCAGAAACTT TTGATAGTGG AAGGTTGGCT GGATGGGTCT 300

TATCMAAARC AAAGAAAGAT GACATGGATG AGGAAATTTC AATATWCGAT GGAAGATGGG 360

AAATTGAAGA GTTGAMAGAA AACCAGGTAC CTGGTGACAG AGGACTGGTA TTAAAATCT 419

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 57 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met His Phe Gln Ala Phe Trp Leu Cys Leu Gly Leu Leu Phe Ile Ser
1 5 10 15

Ile Asn Ala Glu Phe Met Asp Asp Asp Val Glu Thr Glu Asp Phe Glu
20 25 30

Glu Asn Ser Glu Glu Ile Asp Val Asn Glu Ser Glu Leu Ser Ser Glu
35 40 45

Ile Lys Tyr Lys Thr Pro Gln Pro Ile
50 55

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 94 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 60

AAAAAAAAAA AAAAAAAAAA AAAAAAGCGG CCGC 94

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 399 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CAGAGAGGCT GAGACCAACC CAGAAACCAC CACYTCTCAC GCCAAAGCTC ACACCTTCAG 60

CCTCCAACAT GAAGGTCTCC GCAGCACTTC TGTGGCTGCT GCTCATAGCA GYTGCCTTCA 120

GCCCCCAGGG GCTCGCTGGG CCAGCTTCTG TCCCAACCAC CTGCTGCTTT AACCTGGCCA 180

ATAGGAAGAT ACCCCTTCAG CGACTAGAGA GCTACAGGAG AATCACCAGT GGCAAATGTC 240

CCCAGAAAGC TGTGATCTTC AAGACCAAAC TGGCCAAGGA TATHTGTGCC GACCCCAAGA 300

AGAAGTGGGT GCAGGATTCC CATGAAGTAT CTGGACCAAA AATCTCCAAC TCCAAAGCCA 360

TAAATAATCA CCATTTTNGA AACCAAAAAA AAAAAAAAA 399

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Lys Val Ser Ala Ala Leu Leu Trp Leu Leu Leu Ile Ala Xaa Ala
1 5 10 15

Phe Ser Pro Gln Gly Leu Ala Gly Pro Ala Ser Val Pro Thr Thr Cys
20 25 30

Cys Phe Asn Leu Ala Asn Arg Lys Ile Pro Leu Gln Arg Leu Glu Ser
35 40 45

Tyr Arg Arg Ile Thr Ser Gly Lys Cys Pro Gln Lys Ala Val Ile Phe
50 55 60

Lys Thr Lys Leu Ala Lys Asp Ile Cys Ala Asp Pro Lys Lys Lys Trp
65 70 75 80

Val Gln

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 448 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GATTTCGAAT TCGGCCAAAG AGGCCTACAA GGGACTAGCA GGCCTAGGGA TACCCTTCCT 60

CTATGGCTCC AGTGTCCCAG CTGCCCCCGC TGCCTACCAT GGCAGGAGCA TGCTCCCTGC 120

CGGTGACCTG CATTTTCACA GAAGCACCCK CAGAAACCTT CAGGGAAACC CCATGCTAGC 180

GGCAACTGCA CCACACTTTG AGGAGAGCTG GGGGCAGAGA TGTNGTCGAC TCAGGAAAAA 240

TACAGGGAAT CAAAAAGCTC TAGACAGTGA TGCTGAGAGT TCCAAAAGTC AAGCAGAAGA 300

AAAAATCCTA GGTCAGACTT ATGCAGTTCC CTATGAAGAC GATCATTATG CAAAAGACCC 360

AGACATTGAA GCACCCAGCA ACCAGAAGTC AAGTGAAACG AATGAAAAGC CAACGACAGC 420

TCTTGCCAAC ACCTGTGGAG AGCTCGAG 448

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Leu Pro Ala Gly Asp Leu His Phe His Arg Ser Thr Xaa Arg Asn
1 5 10 15

Leu Gln Gly Asn Pro Met Leu Ala Ala Thr Ala Pro His Phe Glu Glu
20 25 30

Ser Trp Gly Gln Arg Cys Xaa Arg Leu Arg Lys Asn Thr Gly Asn Gln
35 40 45

Lys Ala Leu Asp Ser Asp Ala Glu Ser Ser Lys Ser Gln Ala Glu Glu
50 55 60

Lys Ile Leu Gly Gln Thr Tyr Ala Val Pro Tyr Glu Asp Asp His Tyr
65 70 75 80

Ala Lys Asp Pro Asp Ile Glu Ala Pro Ser Asn Gln Lys Ser Ser Glu
85 90 95

Thr Asn Glu Lys Pro Thr Thr Ala Leu Ala Asn Thr Cys Gly Glu Leu
100 105 110

Glu

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 287 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGCTCACGGC TGTAATCCCA ACACTTTGGG AGTCTGAGGC GGGNGAATCA TGAGGTCAGG 60

AGATTAAGAC CAGCTTGGCC AACATGGTGA AACCCCGTNT NTACTAAAAA TACAAAAAAA 120

TTAGCTAGGC CTGGTGGTGC GCGAATGTAG TCCCAGCTAC TCGGGAGGCT GAAGCAGGAG 180

AATTGCTTGA ACCTGGGAAG CGGAGGCTAC AGTGAGCTGA GATCGTGCCA CTGCACTCCA 240

GCCTGGGTGA CAGAGCAGGA CTCTGTNTCA AAAAAAAAAA AAAAAAA 287

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 228 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGANAGCTGT TCAGCTATGG GTGCTGTCAC ANATTANCTG TATCTTTGNC AGTTTAGCTG 60

GATGCTCATT CAGTCTGTGA ATTTCTGGTA NGTGCTGGTG ATGAATGATG AGCACACAGA 120

GAGGGGATAT CTGCTGTTTT TCCTTCTGAG TTGGGGANTA CCAGCTTTTG TGGTGATTCT 180

CCTCATAGTT ATTTTGAAAG GAATCTATCA TCAGAGCATG TCANAGAT 228

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 541 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GACCTGTNTT TTATTCCAAA CGTCTATNCT GCTTTNTTCA CTGCAGCTNC TTGTTCCTTT 60

GACNTNCCTC NTGNTGGTNT TCNTGGTNTT CATCCATGCC TACCAGGTGA ANCCACANTG 120

GAAAGCATAT GATGATNTNT TCAGAGGAAG GACAAATGCT GCAGAAATTC CACTGATTTT 180

ATATCTCTTT GCTCTGATTT CCNTGACATG GCTTTGGGGA GGACTACACA TGGCCTACAG 240

GCACTTCTGG ATGTTGGTTC TCTTTGTCAT TTTCAACAGT CTGCAGGGAC TTTATGTTTT 300

CATGGTTTAT TTCATTTTWC ACAACCAAAT GTGTTGCCCT ATGAAGGCCA GTTACACTGT 360

GGAAATGAAT GGGCATCCTG GACCCAGCAC AGCCTTTTTC ACGCCCGGGA GTGGAATGCC 420

TCCTGCTGGA GGGGAAATCA GCAAGTCCAC CCAGAATCTC ATCGGTGCTA TGGAGGAGGT 480

GCCACCTGAC TGGGAGAGAG CATCCTTCCA ACAGGGCAGT CAGGCCAGCC CTGATTTAAA 540

G 541

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 104 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met Ala Tyr Arg His Phe Trp Met Leu Val Leu Phe Val Ile Phe Asn
1 5 10 15

Ser Leu Gln Gly Leu Tyr Val Phe Met Val Tyr Phe Ile Xaa His Asn
20 25 30

Gln Met Cys Cys Pro Met Lys Ala Ser Tyr Thr Val Glu Met Asn Gly
35 40 45

His Pro Gly Pro Ser Thr Ala Phe Phe Thr Pro Gly Ser Gly Met Pro
50 55 60

Pro Ala Gly Gly Glu Ile Ser Lys Ser Thr Gln Asn Leu Ile Gly Ala
65 70 75 80

Met Glu Glu Val Pro Pro Asp Trp Glu Arg Ala Ser Phe Gln Gln Gly
85 90 95

Ser Gln Ala Ser Pro Asp Leu Lys
100

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 238 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CCTGTGAATT NTACTGGATG ATTAATACAA ACGTGATTGT TGTATTTGGA GTATAAATTA 60

CTGATTGTAT GTNACCTGAA AATTCACTGC TATAAGAAAG GTGGANTCAG TTTGTATCAN 120

TTAATAGGAT TTTCATATTC CAAGGATATT AGTTGTTTTT TTAATCATCC TATATGGCTA 180

ACATTGTTTA ATGAAAGTAA TAATCAATAA AGCAATAGAA TCTAAAAAAA AAAAAAAA 238

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 265 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

TTGCTGTTGC GCGGGATGGT GGATGACTTG TCAAACTCGG GCGGGCCCTC GCTGTCCGCA 60

TCCCCATTCA CGGAGTANCA NTCGTANTCN GAGCCTGGGG GCACGGGACA CANTGAGGCC 120

CANGGCCCAN GTGGCCCCTT GCCCCCAGCC CACCAGGGTG AGCACAGAGG GGGAAGGACG 180

GGGCCCTCCT GGATGGCTAA NTCCCANCTG TCCCTGGTCC CACCCCANCC CCGCGGGCCT 240

GCCTTGGGAA GGGATGGTGT CCTCA 265

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 467 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GCAGGAAATC TGGGGATCTA AATCCAGAAT GATTCAGAGA GCTGGAGGAA GGGGGCTGCC 60

CTGGCTTAAC TTGGTTCATT CCCAGGCCAA CACCTCACCG TGATCCACGT CCCCACTGCT 120

GTGCTGAAGC TGGNGTNTGC CCCAGGGAAC CCTGCCGGTC ACACATGYTC AGGATTTCAT 180

GGGCCTGTGT CNACCCTGCT TTTTTCTTTA TTCTTNGTAG TNGTTTAGGA GTGGGGGGCC 240

TCGCAGAACA CNTAGTCCAG CCCACTGCCC AGAGCAGGTG TGTCCCTTTC ATAMTTCAGT 300

CCACTTTAAA ACAGCCTTCC CCCACCCCCT TYTATGGTAG CAGTTYTCCT CGGGGTYTCC 360

ATGGACACCC TGTGCCCCAA GCCGATGGCC CCACCCAGCA GCATCAGCAC AGCTGCCCCC 420

CTTYTCCGCA GAGCAGGCTY TCCTTTACGG GAMTYTCCTY TTCCCTC 467

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Phe Phe Phe Ile Leu Xaa Ser Xaa Leu Gly Val Gly Gly Leu Ala Glu
1 5 10 15

His Xaa Val Gln Pro Thr Ala Gln Ser Arg Cys Val
20 25

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 279 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GGGAGGCTGA NGCATAAGGA TCACTTGAGC CCAGGAGTTC ANGACCAGCC TAACATAGTG 60

AGACCCCTGA NTTTACAAAA AATTAAAGTT AGCCAGGTGT GGTGGNACAN GCCTGTGGTC 120

CCAGCTACAC AGGAAGCTGA GGCAGGAGGA TATNTTGAGC CTAGGAATTC AAGGCTGCAG 180

NGAGCTGTGA TNACACCACT GAACTCCTGA ACTCCAGTGT GCGTGACAGA GCAAGACTCT 240

GTNTCNAAAN AAAAANAAAA AAAAAAAAAA GCGGCCGCT 279

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 233 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

AAGCCCCCCA CGCCCCGAGC CCACCCTGCT CACCGGCCTC TGCCCGAGTT CCCCGCATAG 60

TGTGGGAGTG TGGANCATCC TANCTTTTCC CCAGCGCCCA GTTCTTTCAC TCTCACTGGA 120

GTCCTGCAGG GACAGCTCGG GCACCATGTA NGCCCGGGTG GGCGTGGGGG CTCACCTANC 180

TCGGTGGTGA ACAGCTGGCA CGTCTCTGGG TTGCGGACGG TAAAGGCCAC GTA 233

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 579 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

ACGNGNGNTC CATCGCCAGA ATTCCNGTNG TNTCAGGAAT GTTCAATAGA TGGAATCCTG 60

TGTGGCCTGA GANGAGTGTT TTTCATGCCG NGTGACACCC TNGAGGCCCG NGCAACTGTT 120

GGTANGTCAA CAGTTAGCTG CTTCTCATTG CNGAGTGGCG ATTGGTCCTG TCATGGTTTA 180

TTCAGCCATG NGGNGGATGG CTACTTGTTT TNTAAGCCAC TTGCCTTCTG ATCGCTGGAC 240

NGACTCTYTC GCCYTYTCTT GGTGCAGTCC TCAGGAGGCT CGGTCACAYT CTCCAAGAGC 300

ACAGCCATCA TCTCCCACGG TACCACAGGC CTGGTCACAT GGGATGCCGC CCTYTACCTT 360

GCAGAATGGG CCATCGAGAA CCCGGCAGCC TTCATTAACA GGTGACCTCG GGGCACAGGG 420

CAGGGCACCG AGGCAGGCTT ACCCTGGTGC AGTCGAAAAC ACGGTCCCCT TTCCTCCCGC 480

CAGGACTGTC CTAGAGCTTG GCAGTGGTGC CGGCCTCACA GGCCTTGCCA TYTGCAAGAN 540

GTGCCGCCCC CGGGCATACA TYTTCAGCGA CCCTCACAG 579

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Met Val Tyr Ser Ala Met Xaa Xaa Met Ala Thr Cys Phe Xaa Ser His
1 5 10 15

Leu Pro Ser Asp Arg Trp Thr Asp
20

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 60

AAAAAAAAAA AAAAAAAAAG CGGCCGC 87

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 224 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GCTTTTTTTT TTTTTTTTGT ATCTTTCTAG TTCATTCTGT CCATTGNTAN TTTTTTATAA 60

ANAAAATTTC ACTACCATAT ACTTTCTGTT CCANANACAG GAAACTGTTT GCAGGTCCCT 120

GAACCTACCT TCATTTTCTA GTGCTGTGCA TTTCCTCATT TCTTTCATTT GGAAANTGGT 180

GAAAANGTCC TCTAACTTGC TTCTTGCCCT CATTTCTCTA AGCA 224

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 593 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TGTTCTTCNG GCACTTCCCA TCACCGNGAT AGCATATTTC ACTGGGGTGG TTTCCATTCC 60

CATTTCCTCT ACTATAGTGA GCCACTGGAG GCGAGAACCC TNGTATTTCC AACATTGGTG 120

TACTCAGCAT CTTGCGTCGA GGACTCAGTA AGTATTATAT TTGAATTCCC ACTGCACCGC 180

TCTAATTAGA ATTTTAAAAA TCACTTTCTA TGTGGATTGT NACACACTTT TTTTCCCCTT 240

AATTCATTTT TCTCCANGNA CTACCCATAT GCATCCTATA TAAATTTACC AGCACTCATA 300

AAAATCTTAC TCAGAAATCT TCAGAGGTTT GCTAAGGATA CAATTTGATT CTTACACATT 360

TAATGCTCAC CAGCTGCTTA GGCCCACACC ATTTATCCAC CCTGATTTGC TACTGCTCTT 420

TGAAATACAA CCAGTGTTTC AGCCAGACTG TTTTCCTGCT TCTGCTCCCC TTCTCCTCCT 480

CCCAGCACAT CTGTGAATTC TTTGACTGGT TTACCACTCC CAMACTCCTC CCCAGCAATG 540

CAGATCTTCT ACACCCTTTA GGATCTAAGC TAAGTCTGCT TCCCAGATAT CCT 593

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Met Leu Thr Ser Cys Leu Gly Pro His His Leu Ser Thr Leu Ile Cys
1 5 10 15

Tyr Cys Ser Leu Lys Tyr Asn Gln Cys Phe Ser Gln Thr Val Phe Leu
20 25 30

Leu Leu Leu Pro Phe Ser Ser Ser Gln His Ile Cys Glu Phe Phe Asp
35 40 45

Trp Phe Thr Thr Pro Xaa Leu Leu Pro Ser Asn Ala Asp Leu Leu His
50 55 60

Pro Leu Gly Ser Lys Leu Ser Leu Leu Pro Arg Tyr Pro
65 70 75

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 256 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TCNTGNATTT AATTATTTAA GCTATATTAA AAAAATTGAA ACCCTTAGAT GTTAATTAAT 60

TTTAAAAACT ANTGATNGAT GCAGNTAAGC TAGAATGATT GGATCAAATC TCACACACAA 120

ATGAGTTTAT TCTTTAAAAA AAAATTTTTT TTTTAGAGAC GGNTTCTTGC TATGTTCCCC 180

AGGATGTTCT TGAACTCATG ACCTCAAGCA ATCCTCCTCC CTCACCCTAC CTGAATTAAA 240

AAAAAAAAAA AAAAAA 256

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

AATGATCAGG ATCTAAGTGT TAGGCGGA 28

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GGTTTCCCTA GTTGAGTCCT CAGGTCCT 28

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

TATCAAGGCA GTTGCTTCTA CTCCTGGG 28

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

ACAAGATGAA ATTGATAGCA AATGCGAC 28

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

ACCTGCTGGA GTCAGCCAAG ATGTTTA 27

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GAATGGGACT CCAAGCCTGC CTCCTA 26

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

TGAGATGAAC AGAAGACCCA AACATAGC 28

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

TCTCACGCCA AAGCTCACAC CTTCAGC 27

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TTGGGTCTTT TGCATAATGA TCGTCTTC 28

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GAACTGGCCT TCATAGGGCA ACACATTT 28

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

AACCCCGAGG AGAACTGCTA CCATAGAA 28

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TCTCGATGGC CCATTCTGCA AGGTAGAG 28

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GTTGTATTTC AAAGAGCAGT AGCAAATC 28

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2 from nucleotide 351 to nucleotide 506;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AZ302_1 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AZ302_1 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AZ302_1 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AZ302_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:3;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:3 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

2. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein, which comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying the protein from the culture

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:3;

(b) fragments of the amino acid sequence of SEQ ID NO:3; and

(c) the amino acid sequence encoded by the cDNA insert of clone AZ302_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:3.

10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:3 from amino acid to amino acid .

11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. The gene corresponding to the cDNA sequence of SEQ ID NO:2, SEQ ID NO:1 or SEQ ID NO:4 .

14. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 23 to nucleotide 517;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AU139_2 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AU139_2 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AU139_2 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AU139_2 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 35 to amino acid 115;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone AU139_2 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

16. The gene corresponding to the cDNA sequence of SEQ ID NO:5 or SEQ ID NO:7.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 288 to nucleotide 629;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 441 to nucleotide 629;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AU105_14 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AU105_14 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AU105_14 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AU105_14 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:9 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i) .

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:9;

(b) the amino acid sequence of SEQ ID NO:9 from amino acid 25 to amino acid 44;

(c) fragments of the amino acid sequence of SEQ ID NO:9; and

(d) the amino acid sequence encoded by the cDNA insert of clone AU105_14 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

19. The gene corresponding to the cDNA sequence of SEQ ID NO:8 or SEQ ID NO:10 .

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 164 to nucleotide 298;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS268_1 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS268_1 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS268_1 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS268_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) fragments of the amino acid sequence of SEQ ID NO:12; and

(c) the amino acid sequence encoded by the cDNA insert of clone AS268_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

22. The gene corresponding to the cDNA sequence of SEQ ID NO:11 or SEQ ID NO:13 .

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 75 to nucleotide 419;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 132 to nucleotide 419;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ147_1 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ147_1 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ147_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ147_1 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) fragments of the amino acid sequence of SEQ ID NO:22; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ147_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

25. The gene corresponding to the cDNA sequence of SEQ ID NO:21 or SEQ ID NO:23 .

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 69 to nucleotide 377;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 120 to nucleotide 377;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AM262_11 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AM262_11 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AM262_11 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AM262_11 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:25;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:25 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:25;

(b) the amino acid sequence of SEQ ID NO:25 from amino acid 14 to amino acid 81;

(c) fragments of the amino acid sequence of SEQ ID NO:25; and

(d) the amino acid sequence encoded by the cDNA insert of clone AM262_11 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

28. The gene corresponding to the cDNA sequence of SEQ ID NO:24.

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide co[illegible]sing the nucleotide sequence of SEQ ID NO:26;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 110 to nucleotide 448;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AR28_1 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AR28_1 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AR28_1 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AR28_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:27 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:27;

(b) the amino acid sequence of SEQ ID NO:27 from amino acid 15 to amino acid 78;

(c) fragments of the amino acid sequence of SEQ ID NO:27; and

(d) the amino acid sequence encoded by the cDNA insert of clone AR28_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

31. The gene corresponding to the cDNA sequence of SEQ ID NO:26 or SEQ ID NO:28 .

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:30;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:30 from nucleotide 230 to nucleotide 541;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS162_1 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS162_1 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS162_1 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS162_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:31;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:31 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:31;

(b) the amino acid sequence of SEQ ID NO:31 from amino acid 5 to amino acid 25;

(c) fragments of the amino acid sequence of SEQ ID NO:31; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS162_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

34. The gene corresponding to the cDNA sequence of SEQ ID NO:30, SEQ ID NO:29 or SEQ ID NO:32 .

35. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 202 to nucleotide 467;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 241 to nucleotide 467;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS264_3 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS264_3 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS264_3 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS264_3 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:35;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:35 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:35;

(b) fragments of the amino acid sequence of SEQ ID NO:35; and

(c) the amino acid sequence encoded by the cDNA insert of clone AS264_3 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

37. The gene corresponding to the cDNA sequence of SEQ ID NO:34, SEQ ID NO:33 or SEQ ID NO:36.

38. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38 from nucleotide 173 to nucleotide 579;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS301_2 deposited under accession number ATCC 98076;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS301_2 deposited under accession number ATCC 98076;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS301_2 deposited under accession number ATCC 98076;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS301_2 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:39;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:39 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

39. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:39;

(b) fragments of the amino acid sequence of SEQ ID NO:39; and

(c) the amino acid sequence encoded by the cDNA insert of clone AS301_2 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

40. The gene corresponding to the cDNA sequence of SEQ ID NO:38, SEQ ID NO:37 or SEQ ID NO:40 .

41. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:42;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:42 from nucleotide 363 to nucleotide 593;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:42 from nucleotide 483 to nucleotide 593;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS86_1 deposited under accession number ATCC 98076;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS86_1 deposited under accession number ATCC 98076;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS86_1 deposited under accession number ATCC 98076;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS86_1 deposited under accession number ATCC 98076;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:43;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:43 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

42. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:43;

(b) fragments of the amino acid sequence of SEQ ID NO:43; and

(c) the amino acid sequence encoded by the cDNA insert of clone AS86_1 deposited under accession number ATCC 98076;

the protein being substantially free from other mammalian proteins.

43. The gene corresponding to the cDNA sequence of SEQ ID NO:42, SEQ ID NO:41 or SEQ ID NO:44 .

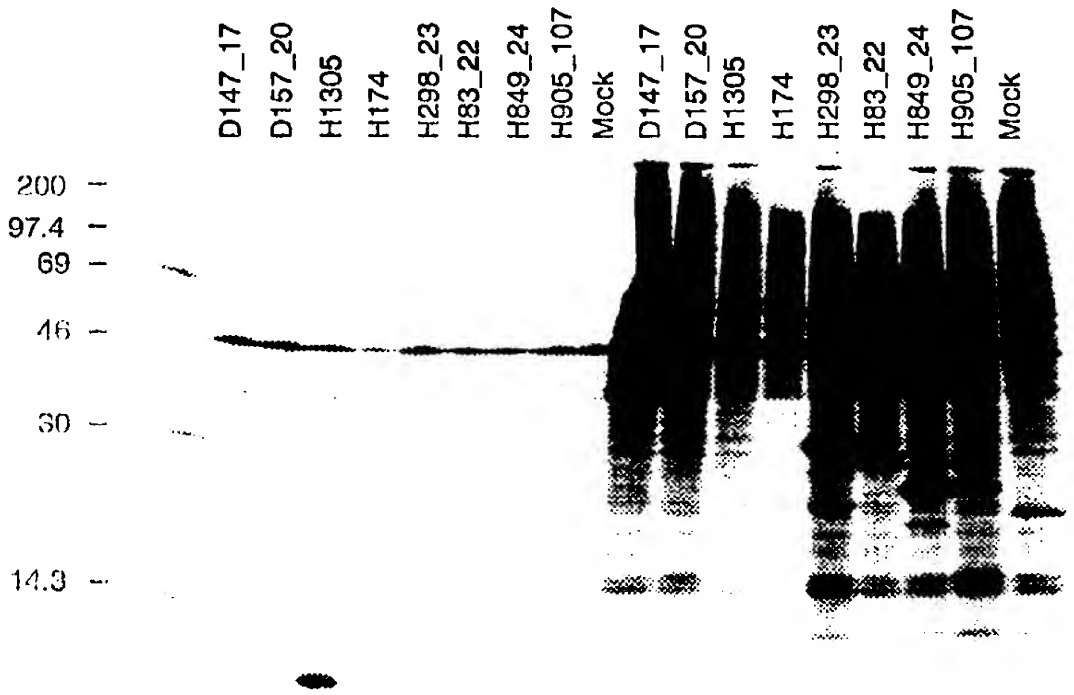
D147_17
D157_20
H1305
H174
H298_23
H83_22
H849_24
H905_107
Mock
D147_17
D157_20
H1305
H174
H298_23
H83_22
H849_24
H905_107
Mock
200
97.4
69
46
30
14.3

Fig. 1
1/2

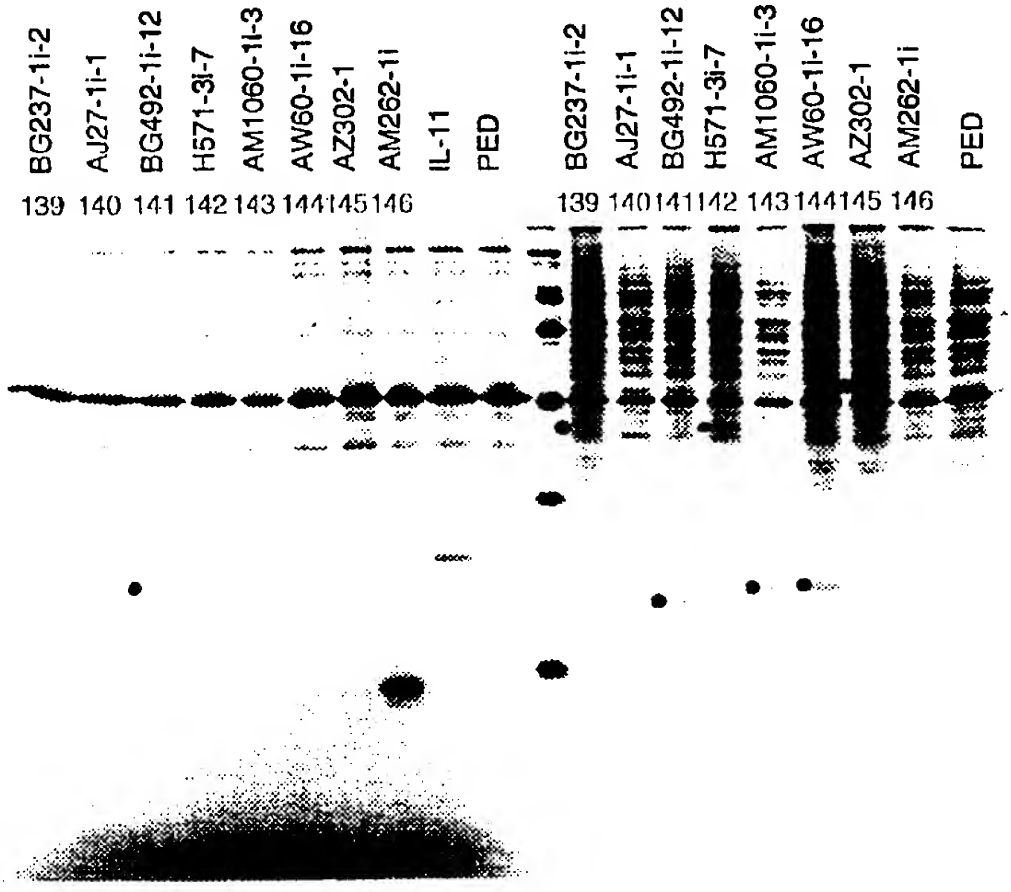
BG237-1i-2
AJ27-1i-1
BG492-1i-12
H571-3i-7
AM1060-1i-3
AW60-1i-16
AZ302-1
AM262-1i
IL-11
PED
139 140 141 142 143 144 145 146
BG237-1i-2
AJ27-1i-1
BG492-1i-12
H571-3i-7
AM1060-1i-3
AW60-1i-16
AZ302-1
AM262-1i
PED
139 140 141 142 143 144 145 146

Fig. 2
2/2

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A3

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(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 90 Green Meadow Drive, Tewksbury, MA 01876 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). EVANS, Cheryl; Apartment #21, 35 Bellvista Road, Brookline, MA 02146 (US). BOWMAN, Michael; 50 Aldrich Road, Canton, MA 02021 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US).

(74) Agent: SPRUNGER, Suzanne, A.; Genetics Institute, Inc., 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(81) Designated States: AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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(54) Title: POLYNUCLEOTIDES ENCODING SECRETED PROTEINS

(57) Abstract

The invention provides 13 clones "AZ302-1" isolated from human colon; "AU139-2", "AU105-14", and "AJ147-1" from human adult testes; "AS268-1", "AS264-3", "AS301-2", "AS162-1" and "AS86-1" from human fetal brain; "D147-17" from human PBMC ; "075-9" from human dendritic cells; "AM262-11" from human fetal kidney and clone "AR28-1" from human adult retina comprising polynucleotides encoding secreted proteins, using methods selective for cDNAs encoding secreted proteins.

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/09878

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 C12N15/19 C07K14/52 A61K38/19
C12N5/10 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JACOBS K ET AL: "A NOVEL METHOD FOR ISOLATING EUKARYOTIC CDNA CLONES ENCODING SECRETED PROTEINS" JOURNAL OF CELLULAR BIOCHEMISTRY - SUPPLEMENT, vol. 21A, 10 March 1995, page 19 XP002027246 see abstract C1-207 ---	
X	J. NATHANS: "69C1 human retina cDNA Tsp509I-cleaved sublibrary Homo sapiens cDNA not directional" EMBL DATABASE ENTRY HSW22546, ACCESSION NUMBER W22546, 9 May 1996, XP002046017 see abstract --- -/--	1,13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 1997	10.03.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	LE CORNEC N.D.R.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/US 97/09878

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CALLARD R E ET AL: "AIMS OF THE BOOK" CYTOKINE FACTSBOOK, 1994, CALLARD R E;GEARING A J H, pages 2/3, 31-38, 64/65, 75/76, 97/98, 148 - 151, 252/253, XP002039160 ---	
P,X	L. HILLIER ET AL: "The WashU-Merck EST project. zo29g02.r1 stratagene colon(#937204) Homo sapiens cDNA clone 588338 5'" EMBL DATABASE ENTRY HSAA51630 , ACCESSION NUMBER AA151630, 15 December 1996, XP002046018 see abstract ---	1,8-10, 13
A	ENG MONG LIM ET AL: "IDENTIFICATION OF MYCOBACTERIUM TUBERCULOSIS DNA SEQUENCES ENCODING EXPORTED PROTEINS BY USING PHOA GENE FUSIONS" JOURNAL OF BACTERIOLOGY, vol. 177, no. 1, 1 January 1995, pages 59-65, XP000560419 ---	
A	M. YOKOYAMA-KOBAYASHI ET AL: "A signal sequence detection system using secreted protease activity as an indicator" GENE., vol. 163, 1995, AMSTERDAM NL, pages 193-196, XP002046435 ---	
T	US 5 536 637 A (JACOBS KENNETH) 16 July 1996 ---	
A	TASHIRO K ET AL: "SIGNAL SEQUENCE TRAP: A CLONING STRATEGY FOR SECRETED PROTEINS AND TYPE I MEMBRANE PROTEINS" SCIENCE, vol. 261, 30 July 1993, pages 600-603, XP000673204 ---	
T	K. A. JACOBS ET AL: "A genetic selection for isolating cDNAs encoding secreted proteins" GENE., vol. 198, 1 October 1997, AMSTERDAM NL, pages 289-296, XP002045919 -----	

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/09878

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 12 is directed to a method of treatment of the human/animal body (Rule 39.1 IV PCT), the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see continuation-sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-13

Polynucleotide sequence as in Seq. ID.2 from clone Az302-1 encoding secreted protein as in Seq. ID.3, fragments, compositions, potential therapeutic use and gene corresponding to the cDNA sequence ID.2, 1 or 4.

2. Claims: 14-16

Polynucleotide sequence as in Seq. ID.5 from clone AU139-2 encoding secreted protein as in Seq. ID.6, fragments, compositions and gene corresponding to the cDNA sequence ID.5 or 7.

3. Claims: 17-19

Polynucleotide sequence as in Seq. ID.8 from clone AU105-14 encoding secreted protein as in Seq. ID.9, fragments, compositions and gene corresponding to the cDNA sequence ID.8 or 10.

4. Claims: 20-22

Polynucleotide sequence as in Seq. ID.11 from clone AS268-1 encoding secreted protein as in Seq. ID.12, fragments, compositions and gene corresponding to the cDNA sequence ID.11 or 13.

5. Claims: 23-25

Polynucleotide sequence as in Seq. ID.21 from clone AJ147-1 encoding secreted protein as in Seq. ID.22, fragments, compositions and gene corresponding to the cDNA sequence ID.21 or 23.

6. Claims: 26-28

Polynucleotide sequence as in Seq. ID.24 from clone AM262-11 encoding secreted protein as in Seq. ID.25, fragments, compositions and gene corresponding to the cDNA sequence ID.24.

7. Claims: 29-31

Polynucleotide sequence as in Seq. ID.26 from clone AR28-1 encoding secreted protein as in Seq. ID.27, fragments, compositions and gene corresponding to the cDNA sequence ID.26 or 28.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

8. Claims: 32-34

Polynucleotide sequence as in Seq. ID.30 from clone AS162-1 encoding secreted protein as in Seq. ID.31, fragments, compositions and gene corresponding to the cDNA sequence ID.30, 29 or 32.

9. Claims: 35-37

Polynucleotide sequence as in Seq. ID.34 from clone AS264-3 encoding secreted protein as in Seq. ID.35, fragments, compositions and gene corresponding to the cDNA sequence ID.34, 33 or 36.

10. Claims: 38-40

Polynucleotide sequence as in Seq. ID.38 from clone AS301-2 encoding secreted protein as in Seq. ID.39, fragments, compositions and gene corresponding to the cDNA sequence ID.38, 37 or 40.

11. Claims: 41-43

Polynucleotide sequence as in Seq. ID.42 from clone AS86-1 encoding secreted protein as in Seq. ID.43, fragments, compositions and gene corresponding to the cDNA sequence ID.42, 41 or 44.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern tal Application No
PCT/US 97/09878

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5536637 A	16-07-96	US 5712116 A	27-01-98

ID **AAV05729**
CS 260d9a38ffda1b68030c79ee7e8451ec
IDH AAV05729 standard; cDNA; 399 BP.
MO DNA
DV DNA
DT1 05-JUN-1998 (first entry)
DT 05-JUN-1998
AK **PATENT** **WO9746683-A2**
AK PRIMARY AC AAV05729
EAK
DR P-PSDB AAW44721
DR WPI 1998-042191/04
EDR
DE Nucleotide sequence of clone AM262_11.
KW Secreted protein
KW antibody
KW ds
KW eotaxin precursor
KW immunoassay reagent
KW nutritional supplement
KW therapeutic activity
EKW
OS Homo sapiens.
SC 4a22b9fcfbf65eca55a08e9eb4312eae
SP HOMO SAPIENS
ESP
INST (GEMY) GENETICS INST INC
CC The present sequence represents the nucleotide sequence of clone
CC AM262_11. The clone was isolated from a human fetal kidney cDNA
CC library using probe AAV05756. AM262_11 is a full length clone, encoding
CC a secreted protein. AM262_11 has some identity with the human eotaxin
CC precursor gene and protein. As such, the AM262_11 protein may share
CC some activity. The nucleic acid can be used for expression
CC of recombinant proteins, as tissue, molecular weight or chromosome
CC markers, indicators of genetic disorders and sources of probes and
CC primers. They can also be used to generate anti-protein or anti-DNA
CC antibodies and as components of interaction trap assays etc. The
CC protein is useful for raising antibodies, as immunoassay reagents
CC and as nutritional supplements. The protein may possibly have any of a
CC great variety of therapeutic activities.
ECC
RN 1 055b2aee3106c985dd7d09b2ff82413e
RC **PD: 11-DEC-1997. PF: 06-JUN-1997; 97WO-US09878. PR: 07-JUN-1996; 96US-0659224.**
RT Nucleic acids encoding secreted proteins from clones within ATCC 98076 - useful as immuno-modulators, anti-proliferative agents, regulators of cell differentiation and tissue growth, etc
RL Patent: WO9746683-A2. Claim 26; Pages 67-68; 99pp; English.
RA Bowman M. BOWMAN M
RA Evans C. EVANS C
RA Jacobs K. JACOBS K
RA Lavallie E.R. LAVALLIE ER
RA McCoy J.M. MCCOY JM
RA Merberg D. MERBERG D
RA Racie L.A. RACIE LA
RA Spaulding V. SPAULDING V
RA Treacy M. TREACY M
ERN
FK CDS
LOC 69..314
LO 69 P 314 P 69 314 +

```
FQ     note
FQ     tag
QD     a
NT     no stop codon given
EFK
SQH    Sequence 399 BP; 125 A; 119 C; 80 G; 71 T; 4 other;
SL     399   9751022155a4ed64703d2dcb13a7e739
SQ     cagagaggctgagaccaacccagaaaccaccacytctcacgccaaagctcacaccttcag
SQ     cctccaacatgaaggtctccgcagcacttctgtggctgctgctcatagcagytgccttca
SQ     gcccccaggggctcgctgggccagcttctgtcccaaccacctgctgctttaacctggcca
SQ     ataggaagataccccttcagcgactagagagctacaggagaatcaccagtggcaaatgtc
SQ     cccagaaagctgtgatcttcaagaccaaactggccaaggatathtgtgccgaccccaaga
SQ     agaagtgggtgcaggattcccatgaagtatctggaccaaaaatctccaactccaaagcca
SQ     taaataatcaccattttngaaaccaaaaaaaaaaaaaaa
ESQ
```

NCBI-BLASTN 2.0.10 [Aug-26-1999]

Reference: Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schaffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.

Query= PF-0027US_SEQ ID NO:1_228187
(291 letters)

Database: Geneseq.NA.2002AUG30
2,085,897 sequences; 1,057,821,503 total letters

Searching.....done

Sequences producing significant alignments:		Score (bits)	E Value
GSEQ:AAT33527	Pancreas expressed chemokine-1 gene.	577	e-163
GSEQ:AAT58777	Human eotaxin cDNA.	569	e-160
GSEQ:AAT62944	Human eosinocyte CC type chemokine eotaxin cDNA	569	e-160
GSEQ:AAV05729	**Nucleotide sequence of clone AM262_11.**	**547**	**e-154**

>**GSEQ:AAV05729** Nucleotide sequence of clone AM262_11.
Length = 399

Score = 547 bits (276), Expect = e-154
Identities = 288/292 (98%), Gaps = 1/292 (0%)
Strand = Plus / Plus

```
Query: 1   atgaaggtctccgcagcacttctgtggctgctgctcatagcagctgccttcagcccccag 60
           ||||||||||||||||||||||||||||||||||||||||| ||||||||||||||||
Sbjct: 69  atgaaggtctccgcagcacttctgtggctgctgctcatagcagytgccttcagcccccag 128


Query: 61  gggctcactgggccagcttctgtcccaaccacctgctgctttaacctggccaataggaag 120
           |||||| ||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 129 gggctcgctgggccagcttctgtcccaaccacctgctgctttaacctggccaataggaag 188


Query: 121 ataccccttcagcgactagagagctacaggagaatcaccagtggcaaatgtccccagaaa 180
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 189 ataccccttcagcgactagagagctacaggagaatcaccagtggcaaatgtccccagaaa 248


Query: 181 gctgtgatcttcaagaccaaactggccaaggatatctgtgccgaccccaagaagaagtgg 240
           |||||||||||||||||||||||||||||||| ||||||||||||||||||||||||
Sbjct: 249 gctgtgatcttcaagaccaaactggccaaggatathtgtgccgaccccaagaagaagtgg 308


Query: 241 gtgcaggatt-ccatgaagtatctggaccaaaaatctccaactccaaagcca 291
           |||||||||| ||||||||||||||||||||||||||||||||||||||
Sbjct: 309 gtgcaggattcccatgaagtatctggaccaaaaatctccaactccaaagcca 360
```

GSEQ: AAV05729 Contd.

Database: Geneseq.NA.2002AUG30
    Posted date: Sep 4, 2002 11:15 AM
  Number of letters in database: 1,057,821,503
  Number of sequences in database: 2,085,897

Lambda	K	H
1.37	0.711	1.31

Gapped

Lambda	K	H
1.37	0.711	1.31

Matrix: blastn matrix:1 -3
Gap Penalties: Existence: 5, Extension: 2
Number of Hits to DB: 210948
Number of Sequences: 2085897
Number of extensions: 210948
Number of successful extensions: 65457
Number of sequences better than 10.0: 201
length of query: 291
length of database: 1,057,821,503
effective HSP length: 19
effective length of query: 272
effective length of database: 1,018,189,460
effective search space: 276947533120
effective search space used: 276947533120
T: 0
A: 0
X1: 6 (11.9 bits)
X2: 10 (19.8 bits)
S1: 12 (24.3 bits)

ID AAW44721
CS f3e59aa16dc0133c416afa8574a7622d
IDH AAW44721 standard; Protein; 82 AA.
MO PRT
DV PRT
DT1 05-JUN-1998 (first entry)
DT 05-JUN-1998
AK PATENT WO9746683-A2
AK PRIMARY AC AAW44721
EAK
DR N-PSDB AAV05729
DR WPI 1998-042191/04
EDR
DE Amino acid sequence of the secreted protein encoded by clone AM262_11.
KW Secreted protein
KW antibody
KW eotaxin precursor
KW immunoassay reagent
KW nutritional supplement
KW therapeutic activity
EKW
OS Homo sapiens.
SC 4a22b9fcfbf65eca55a08e9eb4312eae
SP HOMO SAPIENS
ESP
INST (GEMY) GENETICS INST INC
CC The present sequence represents the amino acid sequence of a
CC secreted protein encoded by clone AM262_11. The clone was isolated
CC from a human fetal kidney cDNA library using probe AAV05756. AM262_11
CC has some identity with the human eotaxin precursor gene and protein.
CC As such, the AM262_11 protein may share some activity. The nucleic
CC acid can be used for expression of recombinant proteins, as tissue,
CC molecular weight or chromosome markers, indicators of genetic disorders
CC and sources of probes and primers. They can also be used to generate
CC anti-protein or anti-DNA antibodies and as components of interaction
CC trap assays etc. The protein is useful for raising antibodies, as
CC immunoassay reagents and as nutritional supplements. The protein may
CC possibly have any of a great variety of therapeutic activities.
ECC
RN 1 e2f23346874f0e3b7ec489e22a8bc8ef
RC **PD: 11-DEC-1997**. PF: 06-JUN-1997; 97WO-US09878. PR: 07-JUN-1996; 96US-0659224.
RT Nucleic acids encoding secreted proteins from clones within ATCC 98076 - useful as immuno-modulators, anti-proliferative agents, regulators of cell differentiation and tissue growth, etc
RL Patent: WO9746683-A2. Claim 26; Page 68; 99pp; English.
RA Bowman M. BOWMAN M
RA Evans C. EVANS C
RA Jacobs K. JACOBS K
RA Lavallie E.R. LAVALLIE ER
RA McCoy J.M. MCCOY JM
RA Merberg D. MERBERG D
RA Racie L.A. RACIE LA
RA Spaulding V. SPAULDING V
RA Treacy M. TREACY M
ERN
FK Misc-difference
LOC 15
LO 15 P 15 P 15 15 +
FQ note
NT not specified
SQH Sequence 82 AA;
SL 82 5c477cf089e8cb2acb17a9deefe7e256
SQ mkvsaallwllliaxafspqglagpasvpttccfnlanrkiplqrlesyrritsgkcpqk
SQ avifktklakdicadpkkkwvq
ESQ

NCBI-BLASTP 2.0.10 [Aug-26-1999]

Reference: Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schaffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.

Query= PF-0027US_SEQ ID NO:2_228187
(97 letters)

Database: Geneseq.AA.2002AUG30
887,419 sequences; 130,709,309 total letters

Searching.....done

Sequences producing significant alignments:		Score (bits)	E Value
GSEQ:AAW00667	Pancreas expressed chemokine-1.	203	3e-52
GSEQ:AAW10099	Human eotaxin.	201	1e-51
GSEQ:AAW14990	Human eosinocyte CC type chemokine eotaxin.	201	1e-51
GSEQ:AAW44721	**Amino acid sequence of the secreted protein enc**	**167**	**1e-41**

> **GSEQ: AAW44721** Amino acid sequence of the secreted protein encoded by clone AM262_11.
Length = 82

Score = 167 bits (419), Expect = 1e-41
Identities = 80/82 (97%), Positives = 80/82 (97%)

```
Query: 1  MKVSAALLWLLLIAAAFSPQGLTGPASVPTTCCFNLANRKIPLQRLESYRRITSGKCPQK
60
          MKVSAALLWLLLIA AFSPQGL GPASVPTTCCFNLANRKIPLQRLESYRRITSGKCPQK
Sbjct: 1  MKVSAALLWLLLIAXAFSPQGLAGPASVPTTCCFNLANRKIPLQRLESYRRITSGKCPQK
60

Query: 61 AVIFKTKLAKDICADPKKKWVQ 82
          AVIFKTKLAKDICADPKKKWVQ
Sbjct: 61 AVIFKTKLAKDICADPKKKWVQ 82
```

GSEQ: AAW44721 Contd.

Database: Geneseq.AA.2002AUG30
    Posted date: Sep 4, 2002 9:25 AM
  Number of letters in database: 130,709,309
  Number of sequences in database: 887,419

Lambda	K	H
0.320	0.133	0.413

Gapped

Lambda	K	H
0.270	0.0470	0.230

Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
Number of Hits to DB: 27383911
Number of Sequences: 887419
Number of extensions: 920834
Number of successful extensions: 3814
Number of sequences better than 10.0: 1205
Number of HSP's better than 10.0 without gapping: 1120
Number of HSP's successfully gapped in prelim test: 85
Number of HSP's that attempted gapping in prelim test: 2081
Number of HSP's gapped (non-prelim): 1205
length of query: 97
length of database: 130,709,309
effective HSP length: 48
effective length of query: 49
effective length of database: 88,113,197
effective search space: 4317546653
effective search space used: 4317546653
T: 11
A: 40
X1: 16 (7.4 bits)
X2: 38 (14.8 bits)
X3: 64 (24.9 bits)
S1: 41 (21.8 bits)